REMARKS

I. Support for Amendments

The specification was amended in order to identify the disclosed sequences with the appropriate SEQ. ID. Numbers. This amendment does not introduce any new subject matter.

The claims were amended to more clearly define the invention. Support for this amendment is found throughout the Specification, for example on page 6, lines 8-30, page 7, lines 1-4, page 10, lines 3 and 4, page 11, lines 12-16, and 27, page 12, lines 6-8, Figure 1b. The amendment is also supported by former claims 2, 9 and 10. Claim 5 was amended in order to more clearly define the CD8 molecule. Support for this amendment can be found in the Specification, for example on page 6, lines 8-11, page 10, lines 3 and 4, and page 11, lines 12-16. Support for newly added claim 24 can be found throughout the Specification, for example, on page 6, lines 25-28. Accordingly, no new matter is added by this Amendment and entry thereof is respectfully requested.

II. Objection to the Oath/Declaration

The Examiner objected to the oath or declaration because it does not identify the mailing or post office address of each inventor. In order to overcome this objection, an application data sheet has been filed herewith in accordance with 37 CFR 1.63(c) and 37 CFR 1.76.

III. Objection to the Specification

The Examiner objected to the specification because the sequences disclosed in the specification, page 6, lines 17 and 22 are not identified with the appropriate SEQ. ID. Numbers.

In order to overcome this objection, the specification has been amended to include the appropriate SEQ. ID. Numbers.

IV. Rejection of claims 1-5 under 35 U.S.C. § 112, first paragraph

Claims 1-5 are rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. Applicants respectfully traverse the rejection. Applicants assert that the claims, as amended, are sufficiently supported by the specification so that one skilled in the art would recognize that applicants had possession of the claimed invention at the time the application was filed.

Applicants assert that the specification includes a sufficient description of the CD8 molecules of the amended claims. As the Examiner stated, the specification does provide a sufficient written description for a particular form of human CD8. The CD8 molecule described in the specification is one that includes an α chain with the sequence disclosed in Figure 1b (SEQ ID NO: 23). The claims have been amended to include this α chain with SEQ ID NO: 23, as well as to CD8 molecules that include specific modifications to this α chain.

The written description of this application clearly allows persons of ordinary skill in the art to recognize that the inventor invented what is claimed. Withdrawal of the rejection of claims 1-5 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

V. Rejection of claim 3 under 35 U.S.C. § 112, second paragraph

Claim 3 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In view of the cancellation of claim 3, withdrawal of the rejection is respectfully requested.

VI. Rejection of claims 1-5 under 35 U.S.C. § 102(b)

The Examiner has rejected claims 1-5 under 35 U.S.C. § 102(b) as being anticipated by Tykocinski et al. (U.S. Patent No. 5,242,687) or Tykocinski et al. (U.S. Patent No. 5,601,828) or Tykocinski et al. (U.S. Patent No. 5,623,056), which all have identical disclosures.

As noted by the Examiner, Tykocinski et al. define their CD8 molecule as being CD8α. In contrast, claims 1 and 5 define the CD8 molecules to be CD8αα or αβ dimers. In addition, Tykocinski et al. do not teach the use of a CD8 molecule having an α chain with SEQ ID NO: 23 or the variants thereof as defined in claim 1.

Furthermore, the claimed invention is directed to the use of soluble human CD8αα or αβ molecules in inhibiting cytotoxic T cell activity. As noted at page 3, line 22 *et seq,* the invention is based on the surprising discovery that soluble CD8 strikingly inhibits CTL activity, with binding of soluble CD8 to less than 1% of MHC molecules causing the inhibition.
By contrast, Tykocinski et al. is concerned with exploiting the "veto" effect of CD8, namely that CD8 has an immunosuppressive activity when it is associated with a second ligand, which would otherwise function as a cellular activator.

In this regard, the veto effect was postulated to explain the observation that T cells in a mixed group do not, under normal circumstances, kill each other, even though they generally present Class I MHC-peptide complexes. It is believed that the interaction of CD8 molecules on the surface of T cells with either the T cells' own MHC peptide-complex or possibly that of other T cells produces a signal that is contrary to the normal CD8-mediated activation signal. This signal inhibits T cell activation and subsequent killing. As this mechanism involves the transduction of a CD-8 mediated signal to the T cells involved, it is an essential requirement that

the CD8 molecules are presented on the surface of the T cells, rather than in soluble form as provided by the invention. Therefore, the veto effect as described in Tykocinski et al. functions by the induction of a CD-8 mediated signal, whereas the soluble CD8 molecules of the invention function by the inhibition of a CD-8 mediated signal. Accordingly, Tykocinski et al. does not provide any teaching towards the invention of using soluble human CD8αα or αβ molecules in the inhibition of cytotoxic T cell activity. Withdrawal of the rejection of claims 1-5 under 35 U.S.C. § 102(b) over Tykocinski et al. is respectfully requested.

VII. Rejection of claims 1-3 under 35 U.S.C. § 102(b)

The Examiner has rejected claims 1-3 under 35 U.S.C. § 102(b) as being anticipated by Jameson et al. (WO 96/22106).

Jameson at al. does not disclose or suggest peptides having the same sequence as SEQ ID NO: 23 or variants thereof as defined in claim 1. Furthermore, as described on page 6, line 27, the peptides disclosed in Jameson et al. are always less than 25 amino acids in length, while the unmodified dimer of the invention contains about 240 amino acids (i.e. two 120 amino acid chains).[1] In addition, unlike the invention, the peptides disclosed in Jameson et al. are not dimers.

Furthermore, Jameson et al.'s disclosure of the use of CD8 peptides in the inhibition of T cell responses is not an enabling disclosure of the invention. In order to anticipate under §102(b), a prior art reference must be enabling to a person having ordinary skill in the art. For instance, the results presented in Jameson et al. are limited purely to short murine CD8-derived peptides. In Example 2, one of these peptides is said to inhibit lysis of targets in a dose-

[1] The exact number of amino acids can vary depending on the modifications that are made as recited in claim 1.

dependant manner; however, no actual data is given. Similarly, in Example 3, two short murine peptides are said to inhibit lysis of targets in a concentration dependent manner, but no actual data is given. The only data presented is in relation to the experiments described in Examples 4-6. In Example 4, one peptide had to be administered at 0.5 mg/day for 50 days to prevent graft rejection. In examples 5 and 6, no indication of the amount of the short peptide administered is given, although Example 5 does refer to Example 2 in which the peptide was administered at 100 μg/ml. Overall, the data in Jameson et al. is very sparse and difficult to interpret. Hence, Jameson et al. does provide an enabling disclosure for the use of the CD8 αα and αβ dimers of the invention.

In addition, a comparison of the technology disclosed in Jameson et al. with that of the invention further illustrates the fact that Jameson et al. does not teach the claimed invention but is actually directed to different molecules. Since Jameson et al. does not provide an enabling disclosure, Applicants have taken the liberty to refer to the corresponding scientific paper of Choksi et al, (1998) Nature Medicine 4 (3) 309-314, a copy of which was included in the Information Disclosure Statement filed on November 14, 2000. The data generated by Choksi et al. and that presented in the claims cannot properly be compared because they relate to two different systems (murine in the case of Choksi et al. and human in the claims), another indication that Jameson et al. does not teach the claimed invention and its use of a human CD8 molecule.

Figure 8 of the present application summarizes the results of a series of CTL killing assays carried out to titrate the effect of peptide pulsing levels on the ability of soluble human CD8 molecules of the invention to inhibit CTL-mediated cell lysis. Figure 8 contains data generated from a CTL killing assay carried out at an Effector:Target (E:T) ration of 10:1, which

is comparable to two of the data points presented in Figure 2b of Choksi et al. These two figures demonstrate that similar concentrations of Choksi et al.'s SC4 peptide and the soluble human molecules of the claimed invention are required to cause a 50% reduction in CTL killing (approximately 100 μg/ml). Importantly, however, Choksi et al.'s SC4 peptide is 6 amino acids in size, whereas the CD8 molecules of the claimed invention are about 240 amino acids in size.[2] Given this data, it shows that approximately 40 times (240/6) as many SC4 peptides are needed in order to give the same affect as a given number of CD8 molecules of the claimed invention. Therefore, it is apparent that the soluble human CD8 molecules of the claimed invention are a far more potent inhibitor of CTL killing. This observation also suggests that the molecular mechanism by which the CD8 molecules of the claimed invention cause inhibition of CTL killing is different, and more "efficient" than that utilized by Choksi et al.'s SC4 peptide. Consequently, Jameson et al. does not teach towards the surprising effects obtained by the claimed invention.

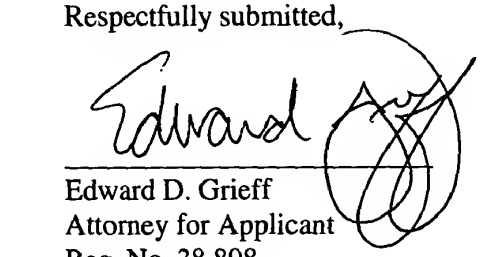
Accordingly, Applicants assert that Jameson et al. does not teach the presently claimed invention for the use of CD8 αα and αβ dimers to inhibit the action of T cell lymphocytes to kill target cells. Applicants respectfully request that the rejection be withdrawn.

[2] The exact number of amino acids can vary depending on the modifications that are made as recited in claim 1.

VIII. CONCLUSION

In view of the foregoing remarks, Applicants believe that the application is in condition for allowance. The Examiner is encouraged to call the undersigned at the number listed below in order to expedite the prosecution of this application.

Respectfully submitted,



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